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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
05/27/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IP.Docketing@aporter.com

Office Action Summary	Application No.	Applicant(s)	
	10/590,211	BUERSTEDDE ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *29,30,35 and 44-73* is/are pending in the application.

4a) Of the above claim(s) *30,57 and 62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29,35,44-56,58-61 and 63-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/12/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Status

Applicants' response of February 12, 2010, to the non-final Office action dated September 10, 2009 has been entered. Claims 29, 58 and 60 have been amended and claims 72 and 73 newly added. No claims were cancelled. Accordingly, claims 29, 30, 35 and 44-73 are pending in the application. Claims 30, 57 and 62 stand withdrawn from further consideration, without traverse, as drawn to non-elected inventions. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01. The claims have been examined commensurate in scope with the elected invention.

Claims 29, 35, 44-56, 58-61 and 63-73 are under current examination.

Withdrawn Claim Rejections - 35 USC § 112- Second Paragraph

Claims 65, 66, 69 and 70 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite and failing to define the metes and bounds of the claims, in the previous Office action dated September 10, 2009. Applicants' arguments that the upper limit of the rate of hypermutation is 1, where every base is mutated with every cell division, are found persuasive. Accordingly, the rejection is hereby withdrawn.

Maintained Claim Rejections - 35 USC § 112- New Matter

Claim 69 and 70 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement, and introducing new matter into the disclosure of an application. The rejection set forth on pp. 3-4 of the previous Office action dated September 10, 2009 is maintained for reasons of record.

The previous Office action indicated that the claims include the limitation "wherein the rate of hypermutation in said genetically modified lymphoid cell is at least ten times higher than the mutation rate in said lymphoid cell". The instant specification is devoid of such description for the newly presented limitations. Applicants state that support for the new claims can be found

in the specification as filed, at least, for example, page 8, lines 12-18. However, the referenced paragraph in the specification discloses only the rates that define hypermutation, i.e. those above background, and spontaneous mutation rates observed in PCR. Background mutation rates include those in non-lymphoid cells. A chicken lymphoid DT cell for example is capable of inducing hypermutation prior to any genetic modification. The cited paragraph is therefore not directed to genetically modified hypermutating lymphoid cells.

Thus, at the time the application was filed, an Artisan of skill would not recognize from the disclosure that Applicant was in possession of genetically modified lymphoid cells having a hypermutation rate at least ten times higher than their non-genetically modified counterpart, as claimed.

Response to Arguments:

Applicants disagree, arguing that ipsis verbis support is not a requirement and that one of ordinary skill in the art would be aware that a hypermutation rate that is ten times higher is directly derivable from page 8, lines 12-18 of the specification. Applicants' arguments have been fully considered, but are not found persuasive.

Applicants' disclosure at page 8 is partially summarized above. That a specific limitation for a hypermutation rate of at least ten times higher may be derivable from "a rate of mutation between 10^{-5} and 10^{-3} bp^{-1} $generation^{-1}$" is not apparent. The terms "at least ten times higher" encompasses hypermutation rates beyond the range that is taught by the disclosure.

Thus, the rejection is maintained for reasons of record and the foregoing response.

New Claim Rejections - 35 USC § 112- New Matter

Applicants' claim amendments have necessitated the following new grounds of rejection.

Claims 29, 60, 72 and 73 are newly rejected are newly rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art (hereafter the Artisan), that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR §1.118 (a) states that

"No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

The claims include the limitation "wherein said transgenic target nucleic acid sequence is in the absence of an adjacent donor sequence capable of serving as a gene conversion donor". The instant specification is devoid of such description for the newly presented limitation. Applicants state that support for the new claims can be found in the specification as filed, at least, for example, page 5, line 37 to page 6, line 1; page 8, lines 1-4; page 11, lines 12-15; page 12, lines 1-6; and page 13, lines 19-22. However, none of the referenced paragraphs address adjacent donor sequences. The closest subject matter (page 11, lines 14-16), refers to an embodiment, wherein "additional nucleic acids capable of serving as gene conversion donors are inserted into the cell genome, preferably upstream of the target nucleic acid". However, such disclosure is distinct from the limitations claimed. Written description rejection is proper only when specification contains no support for negative limitation. *In re Johnson*, 194 USPQ 187, 196 (CCPA 1977). Specification provides no inherent support for the limitation. See MPEP 2164.08 and 2173.05.

Thus, at the time the application was filed, an Artisan of skill would not recognize from the disclosure that Applicant was in possession of transgenic target nucleic acid sequences in the absence of an adjacent donor sequence capable of serving as a gene conversion donor, as claimed.

This is a new matter rejection.

Maintained & New Claim Rejections - 35 USC § 112, Written Description

Applicants' claim amendments have necessitated the following new grounds of rejection.

Claims 29, 35, 44-56, 58-61 and 63-71 stand rejected and claims 72 and 73 are newly rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The rejection set forth on pp. 4-7 of the previous Office action dated September 10, 2009 is maintained for claims 29, 35, 44-56, 58-61 and 63-71, and further applied to claims 72 and 73 for reasons of record.

The claims broadly embrace a method for producing a genetically modified lymphoid cell capable of hypermutation at a rate higher than the hypermutation rate in its non-genetically modified counterpart, wherein the cells contain no deleterious mutations in genes encoding XRCC2, XRCC3, or RAD51 protein, necessitating structure/function relationships.

The specification discloses only one lymphoid cell (chicken DT40 $AID^{R}\psi V^{-}$), that contains no mutations in RAD51 or its analogs, and replaces gene conversion by hypermutation (pp. 16-17 of the substitute specification). The specification is silent however on any other genetically modified variants of lymphoid cells from any species of animals, or a DT40 or similar cell that has a hypermutation rate higher than the rate of its non-genetically modified counterpart that contains ψV donors.

Thus it is clear that Applicants' description of structure and activity regarding other lymphoid cell variants is based in large part on conjecture. The various genetically modified lymphoid cells having a hypermutation rate higher than the rate of its non-genetically modified counterpart that contains ψV donors and RAD51 were not known in the prior art at the time of the instant invention by Applicants, and include lymphoid cell variants yet to be discovered.

As the specification fails to describe the structure and activity for the genus of variants and genetically modified lymphoid cells, the disclosed single species does not constitute a substantial portion of the claimed genus.

The instant specification is devoid of a description for the numerous derivatives and variants of lymphoid cell that retain ψV donors and RAD51 gene activity, but have a hypermutation rate higher than that of a non-genetically modified cell. The specification merely discloses the structure and function of DT40 $AID^{R}\psi V^{-}$ lymphoid cell and lymphoid cells having mutations in the RAD51 gene, such as XRCC3, previously

described in the prior art, with no other variants or derivatives displaying the requisite biological activity. Thus, Applicants have failed to demonstrate possession of the numerous variants or genetically modified derivatives claimed.

Response to Arguments:

Applicants disagree, arguing that the specification demonstrates proof of concept with chicken cell DT40 $AID^{R}\psi V^{-}$, and that Applicants disclose a method of producing a genetically modified lymphoid cell capable of directed and selective genetic diversification of a transgenic target nucleic acid sequence by hypermutation without deleting the endogenous ψV genes, with reference Example 2, on page 19 and Figure 7A. Applicants' arguments have been fully considered, but are not found persuasive.

In response, it should be noted that the prophetic example 2 of the specification exemplifies "a target nucleic acid which can be genetically diversified using the cell system of the invention" (page 19). The specification states: "The AID^{R} and the ψV knock-out DT40 clones are a powerful experimental system to address the role of trans-acting factors and cis-acting regulatory sequences for Ig gene conversion and hypermutation". Thus, it is clear that the cell system of the invention is chicken DT40 $AID^{R}\psi V^{-}$ lymphoid cell system. Further evidence regarding the cell system can be found on page 14 of the specification, stating: "Herein is reported that ablation of ψV donor activates AID-dependent Ig hypermutation in chicken B cell line DT40…Futhermore ψV knock-out DT40 is a proposed as an ideal model system to approach the molecular mechanism of Ig hypermutation and as a new tool for *in situ* mutagenesis." Applicants are invited to explain how hypermutation is activated following ψV donor ablation, when they state that hypermutation is present in the presence of endogenous ψV genes. Applicants' arguments are thus inconsistent with their disclosure, and further in conflict with the teachings of the post-filing art of Arakawa et al. (PLoS Biol. 2:0967-0974; 2004). Further, Applicants with reference to Figure 7C describe the replacement of the endogenous ψV loci. If such loci are not knocked out, then how can they be replaced?

The examiner acknowledges that an unmodified chicken DT lymphoid cell is capable of gene conversion and hypermutation. However, the instant claims require that the cell be capable of hypermutation rates higher than the background mutation rate of the lymphoid cell, and the

only cell system disclosed by the instant specification and the post-filing art capable of doing so is the chicken DT40 $AID^{R}\psi V^{-}$ lymphoid cell system. Applicants should note that the instant claims are not even limited to a lymphoid B cell, but read on any lymphoid cell, that include PCs, T cells, NK cells, stem cells, lymphoblasts and plasma cells. Further, it is well established that many cells are capable of gene conversion, especially when gene duplication is present.

Applicants argue the claimed methods can be applied to any lymphoid cell capable of gene conversion and the specification states that a cell used in the present invention can be any cell that is "constructed by replacing the endogenous V-gene or segments thereof with a transgene."; and that no other modifications are required to use the claimed subject matter.

Such is not found persuasive for the reasons set forth above. Further, it should be noted that while instant claim 29 requires that the target nucleic acid sequence be in the immunoglobulin locus of the lymphoid cell, claim 60 is not so limited. Moreover, base claims 29 and 60 are so broad in scope that they encompass any wild type lymphoid cell, as they require absolutely no mutations or alterations, other than introducing a target sequence to be modified. Moreover, Applicants specifically state: "one of ordinary skill in the art would recognize that any wild-type gene conversion-active cell should be suitable for use in the claimed method". However, a skilled artisan would readily recognize that any wild-type gene conversion-active cell would not be capable of having a hypermutation activity rate higher than the mutation rate of itself, absent the activation of the AID system by removal of ψV donors.

Thus, the rejection is maintained and further applied to claims 72 and 73 for reasons of record and the commentary set forth above.

Maintained & New Claim Rejections - 35 USC § 112-Scope of Enablement

Applicant's claim amendments have necessitated the following new grounds of rejection.

Claims 29, 35, 44-56, 58-61 and 63-71 stand rejected and claims 72 and 73 are newly rejected under 35 U.S.C.§112, first paragraph, because the specification is not considered enabling the full breadth of the claimed invention. The rejection set forth on pp. 7-11 of the

previous Office action dated September 10, 2009 is maintained is maintained for claims 29, 35, 44-56, 58-61 and 63-71, and further applied to claims 72 and 73 for reasons of record.

The previously Office action indicated an enabled claim scope limited to a method for selective genetic diversification of a transgenic target nucleic acid sequence by hypermutation, in a lymphoid cell lacking ψV donors, wherein the lymphoid cell lacking ψV donors is capable of gene conversion prior to deletion of ψV donor sequences, said method comprising introducing a genetic construct comprising said target nucleic acid into the immunoglobulin locus of the lymphoid cell lacking ψV donors, whereby said target nucleic acid sequence is modified by hypermutation at a rate higher than the rate of mutation prior to deletion of ψV donor sequences.

It was previously indicated that the claims therefore lack the requisite method steps that can produce a lymphoid cell having increased hypermutation activity. It was further noted that to produce a genetically modified lymphoid cell (from chicken, rabbit, cows, pigs, excluding humans and mice), capable of increased hypermutation rates, the genes or proteins controlling gene conversion and hypermutation must be selectively modified. Instant claims 29 and 60 only require that the lymphoid cell contain no deleterious mutations in the RAD51 gene or its analogs, and yet be capable of increased rates of hypermutation.

The specification discloses only one lymphoid cell (chicken DT40 $AID^{R}\psi V^{-}$), in the wording examples, that contains no mutations in RAD51 or its analogs, and replaces gene conversion by hypermutation (pp. 16-17 of the substitute specification). The specification is silent however on any other genetically modified variants of lymphoid cells from any species of animals, or a DT40 or similar cell that has a hypermutation rate higher than the rate of its non-genetically modified counterpart that contains ψV donors, other than the RAD51 gene and its analogs. The skilled artisan would therefore need to engage in further additional experimentation to discover a lymphoid cell having the desired characteristics of higher hypermutation rates with no deleterious mutations in RAD51 or its analogs. Such experimentation necessarily has unpredictable outcomes and thus constitutes an undue burden on the skilled artisan.

The prior art of Sale et al. (U.S. Patent Application Publication No.: 2005/0026246; of record) teaches a method for generating diversity by preparing an antibody-producing cell line

capable of directed constitutive hypermutation of a specific nucleic acid region, comprising selecting a cell in which the rate of V gene mutation exceeds that of other gene mutation (Title and Abstract). The authors teach a cell capable of directed constitutive hypermutation as a genetically manipulated chicken DT40 cell that include mutations in the RAD51, RAD52 and Rad54 genes (Example 8). The prior art appears silent however, on producing lymphoid cells having increased hypermutation rates that are capable of gene conversion as precursors, but carry no mutations in genes controlling gene conversion and hypermutation. Thus, the production of such lymphoid cells is not routine and remains unpredictable.

Therefore, a person of skill in the art would need to engage in further experimentation to determine whether the instantly claimed method would could by carried out in a lymphoid cell that is not deficient in its pseudo V genes. The guidance provided by the specification amounts to an invitation for the skilled Artisan to try and follow the disclosed instructions to make and use the claimed invention. At the time of the instant invention, the skilled artisan not have been able to predict without undue experimentation whether the claimed method could be carried out in a lymphoid cell that is not deficient in its pseudo V genes or RAD51 gene and its analogs.

Response to Arguments:

Applicants disagree, and citing MPEP § 2164.04arguing that if the Examiner maintains that deleting the endogenous ψV genes is required, Applicants specifically request that the Examiner provide a basis by directing Applicants to the evidence he relied on. Applicants' arguments have been fully considered, but are not found persuasive.

In response it should be noted that the instant claims require that the cell be capable of hypermutation rates higher than the background mutation rate of the lymphoid cell, and the only cell system disclosed by the instant specification and the post-filing art capable of doing so is the chicken DT40 $AID^{R}\psi V^{-}$ lymphoid cell system.

Applicants refer to the post-filing art of Arakawa et al., Nucleic Acids Research 36(1): el, 2008, showing that the insertion of a GFP transgene into the ψV^{+} Ig locus of a chicken B cell results in the transgene being diversified by hypermutation when endogenous ψV genes are present. Applicants additionally refer to the post-filing art of Blagodatski et al., PLOS Genetics 5(1): el 000332, 2009, to illustrate that GFP inserted into the Ig locus of a lymphoid cell capable

of gene conversion containing endogenous ψV genes was diversified by hypermutation.

Such is not found persuasive, because the issue is not simply the ability of the cells to carry out gene conversion and hypermutation, but rather the ability to hypermutate a target sequence at a rate higher than the background mutation rate of the lymphoid cell. Applicants' arguments are therefore not commensurate with the claimed invention. Applicants should note that MPEP 2164.05(a) states: "Specification Must Be Enabling as of the Filing Date". Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. *In re Gunn*, 537 F.2d 1123, 1128, 190 USPQ 402,405-06 (CCPA 1976); *In re Budnick*, 537 F.2d 535, 538, 190 USPQ 422, 424 (CCPA 1976).

However, MPEP 2164.05(a), also states: If individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered. In *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993). The post-filing art of Arakawa et al. (PLoS Biol. 2:0967-0974; 2004), that includes the inventors of the instant application teaches the stepwise removal of ψV donors not only reduces and eventually abolishes Ig gene conversion, but also activates AID-dependent Ig hypermutation in DT40 B-cell line (Abstract).

It should be yet further noted that the post-filing Blagodatski reference actually indicates that hypermutation of the Ig genes requires the activation of AID, and further Ig-related cis-acting sequences are required to predispose neighboring transcription units to hypermutation (Abstract). The foregoing brings into question the invention of instant claim 60, where the transgene target is inserted into any chromosomal region of a lymphoid cell.

Thus, the rejection is maintained and further applied to claims 72 and 73 for reasons of record and the foregoing commentary.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. The claims are drawn to the same invention claimed earlier in the application and would have been finally rejected on the grounds and art of record in the next Office Action if they had been entered earlier in the application. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR§1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Fereydoun G Sajjadi/
Primary Examiner, Art Unit 1633